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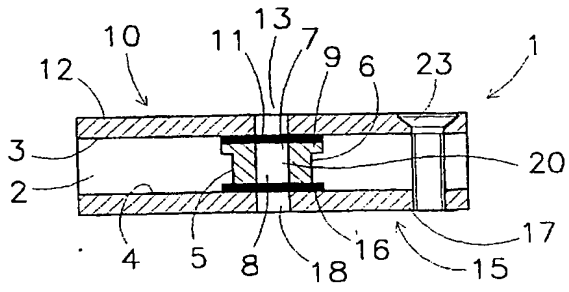
(54) Title: AN ASSEMBLY AND METHOD FOR PERFORMING PARALLEL CHEMICAL EXPERIMENTS, IN PARTICULAR CRYSTALLISATION EXPERIMENTS



(57) Abstract: An assembly and method for performing parallel chemical experiments, in particular crystallisation experiments. The assembly has a main body having a first and a second face on opposite sides thereof. Multiple bores extend through said main body between said first and second face. Tubular liners are provided having openings at opposite ends thereof, each liner removably fitting in a bore in the main body. First closure means close the openings of the liners at the first face of the main body. Second closure means close the openings of the liners at the second face of the main body. The first and second closure means are fastenable to said main body, so that an experimentation chamber is defined within each liner.

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An assembly and method for performing parallel chemical experiments, in particular crystallisation experiments.

The present invention relates to an assembly for performing parallel chemical experiments, in particular crystallisation experiments. The present invention also relates to systems comprising such an assembly as well as methods wherein the assembly is used.

An assembly as well as systems and methods for performing parallel crystallisation experiments are known from WO 02/06802. The known assembly comprises a microplate having multiple microwells having an opening at the top. Sealing of the wells is effected by O-ring seals around the top of each well, which are interpositioned between the microplate and a cover plate.

The known assembly is not sufficiently practical when conducting parallel experiments in high volumes, known as high throughput experimentation. In particular the known assembly is unsatisfactory when conducting parallel crystallisation experiments.

An object of the present invention is to provide an improved experimentation assembly, in particular for use in crystallisation experiments.

The present invention provides an assembly for performing parallel chemical experiments, in particular crystallisation experiments, said assembly comprising:

- a main body having a first and a second face on opposite sides thereof, multiple bores extending through said main body between said first and second face,
- tubular liners having openings at opposite ends thereof, each liner removably fitting in a bore in the main body,
- first closure means for closing the openings of the liners at the first face of the main body,
- second closure means for closing the openings of the liners at the second face of the main body,

- said first and second closure means being attachable to said main body, so that an experimentation chamber is defined within each liner.

The assembly according to the invention allows for the use of tubular liners which are simple to manufacture and also can be cleaned easily prior and/or after the experiment or be simply discarded after use. Also the main body allows for an efficient cleaning of the bores, which is particularly relevant in the field of crystallisation experiments where any contamination is likely to affect the outcome of the experiment.

The present invention also relates to systems comprising the assembly of the invention and methods wherein said assembly is used.

The assembly or system according to the invention can be adavantageously ised for solid form screening of molecules, e.g. salt screening, polymorph screening, enantiomer separation screening, in particular of active pharmaceutical ingredients.

The invention and and preferred embodiments thereof are described in the claims and the following description referring to the drawings. In the drawings:

Fig. 1 shows in cross-section a part of an experimentation assembly according to the present invention,

Fig. 2 shows an embodiment of the first and/or second sealing members of the assembly of figure 1,

Fig. 3. shows a part of a filtration device to be used in combination with the experimentation assembly of the invention,

Fig. 4 shows a collecting device, and

Fig. 5 shows a vapour discharge assembly.

In figure 1 a part of an experimentation assembly 1 for performing parallel chemical experiments, in particular crystallisation experiments, is shown.

The assembly 1 comprises a main body 2 having a first face 3 and a second face 4 on opposite sides thereof and multiple bores 5 extending through said main body 2 between said first face 3 and second face 4.

In the figure 1 only one bore 5 is visible. In practice the number of bores vary depending on the application. Preferably the assembly 1 has at least four bores.

In each of the bores 5 a removable tubular liner 6 is arranged. Each liner 6 has openings 7, 8 at opposite ends thereof. Each liner 6 is removably fitted in a corresponding bore 5 in the main body 2.

The assembly 1 further comprises first closure means 10 for closing the openings 7 of the liners 6 at the first face 3 of the main body 2. Also the assembly comprises second closure means 15 for closing the openings 8 of the liners 6 at the second face 4 of the main body 2.

Said first and second closure means 10, 15 are fixed with respect to said main body 2 using suitable fastening means such as bolts 23, so that an experimentation chamber 20 is defined within each liner 5 which is closed of at its ends as will be explained below.

The first closure means 10 comprise in the embodiment shown here multiple elastic first sealing members 11, corresponding to the nnumber of bores 5, and a first cover plate 12 extending over all the bores 5, so that said first sealing members 11 are interpositioned between the ends of the tubular liners 6 and the first cover plate 12.

The second closure means 15 comprise in the embodiment shown here multiple second elastic sealing members 16 and a second cover plate 17, so that said second sealing members 16 are interpositioned between the ends of the tubular liners 6 and the second cover plate 17.

The first and second sealing members 11,16 are embodied here as a sealing disc or disc shaped septum, which can be pierced by a hollow needle.

The first and second cover plates 11, 17 are each provided with bores 13, 18 extending in line with the bores 5 in the main

body 2, in particular the bore in the liners 6. As the first and second sealing members 11, 16 are pierceable, a needle can be inserted into each experimentation chamber 20 e.g. for purposes explained below.

The tubular liner 6 is provided with an outwardly directed support projection in the form a circumferential support flange 9 at one end of the tubular liner 6. The main body 2 is at the first face 3 provided with an annular recess for receiving said support flange 9 as well as the sealing member 11.

In an embodiment not shown in the drawing the first and/or second sealing members 11, 16 comprise a filter for filtering the contents of the experimentation chamber upon removal of said contents. In a practical embodiment thereof, shown in figure 2, the first and/or second sealing members comprise an annular seal 20, such as an O-ring, and a filter 21, such as a mesh or sheet, extending across the central opening of said seal 20.

Preferably the main body 2 is a solid block, e.g. of stainless steel, brass, hasteloy.

Preferably the main body 2 is made of a heat conducting material, e.g. a metal, and the liners 6 are in contact with said main body essentially over their entire outer surface so that an optimum heat transfer is obtained.

Preferably the volume of the experimentation chamber 20 is at most 1 ml.

Figure 3 shows a part of a filtration device 30 to be used in combination with the experimentation assembly of the invention, e.g. according to figure 1.

The filtration device 30 has channels 31 with inlets 32 corresponding to the bores 5 in the main body 2 of the experimentation assembly 1 and a filter 33 in each channel 31.

The filtration device 30 and the assembly 1 are preferably used so that - after removal of the top cover plate of the experimentation assembly 1 when in horizontal position and removal of the associated sealing member(s) - said filtration device 30 can be brought against the top face of the main body 2, after which said system is reversed and the contents of the experimentation chambers 20 enters the channels 31 in the filtration device 30 and is filtered by the filters 33.

The channels 32 in the filtration device 30 have outlets 34. If the system further comprises a collecting device 40, e.g. as shown in figure 4, having collecting chambers 41 with inlets corresponding to the outlets of the filtration device 30 the filtered contents of the experimentation chambers can enter said collecting chambers 41.

The assembly 1 allows for the efficient use of a press device having multiple press members corresponding to the liners of the experimentation assembly for pressing said liners 6 into and/or out of the bores 5 of the main body 2.

As mentioned before the assembly 1 can be used preferably in combination with heating means, e.g for heating and thereby possibly evaporating a liquid content in the experimentation chambers 20 or for bringing a solid into solution which can the for crystals as it is cooled down.

The heating means can either be mounted in the main body 2 and/or cover plate(s) 12, 18 or be brought into contact with the main body 2 and/or cover plate(s) 12,18.

If evaporation of a part of the content of the experimentation chambers 20 is desired, it is preferred that the system further comprises a vapour discharge assembly 50 e.g. as shown in figure 5.

The assembly 50 comprises multiple hollow needle members 51, which are each adapted to be pierced through a sealing

member 11, 16 so that vapour discharges via said hollow needle 51.

As is shown in figure 5 the needles 51 are preferably upwardly directed and arranged to pierce through the sealing members 16 sealing the bottom face of the experimentation assembly 50 in horizontal orientation. This allows bringing the point of the hollow needles well above a liquid level in the experimentation chambers 20 so that vapour will escape through said needles 51.

It will be clear that the assembly 50 can also be used to drain a part of any liquid contents from the experimentation chambers.

In another embodiment a feed assembly is provided for feeding a substance into the experimentation chambers 20, said feed assembly comprising at least one hollow needle member adapted to be pierced through a sealing member. The introduction into the chambers 20 can be done from below or above.

For instance in the field of crystallisation experiments such a feed assembly allows for the introduction of an anti-solvent into the experimentation chambers.

C L A I M S.

1. An assembly (1) for performing parallel chemical experiments, in particular crystallisation experiments, said assembly comprising:

- a main body (2) having a first (3) and a second face (4) on opposite sides thereof, multiple bores (5) extending through said main body between said first and second face,
- tubular liners (6) having openings (7,8) at opposite ends thereof, each liner removably fitting in a bore in the main body,
- first closure means (10) for closing the openings of the liners at the first face of the main body,
- second closure means (15) for closing the openings of the liners at the second face of the main body,
- said first and second closure means (15,16) being fastenable to said main body, so that an experimentation chamber (20) is defined within each liner (6).

2. Assembly according to claim 1, wherein said first closure means comprise one or more elastic first sealing members and a first cover plate, so that said first sealing members are interpositioned between the ends of the tubular liners and the first cover plate.

3. Assembly according to claim 1 or 2, wherein said second closure means comprise one or more second elastic sealing members and a second cover plate, so that said second sealing members are interpositioned between the ends of the tubular liners and the second cover plate.

4. Assembly according to claims 1, wherein the tubular liners are each provided with at least one outwardly directed support projection and the bores in the main body are each provided with a corresponding recess for receiving the support projection.

5. Assembly according to claim 4, wherein the outwardly directed support projection is a circumferential support flange at one end of the tubular liner and the bores in the main body each form an annular recess for receiving said support flange.

6. Assembly according to claim 2, wherein said first closure means comprise multiple first sealing members, each first sealing member engaging an end face of a liner.

7. Assembly according to claim 6, wherein the first face of the main body and/or the first cover plate is provided with recesses at the locations of the liner ends for receiving a first sealing member.

8. Assembly according to claim 3, wherein said second closure means comprise multiple second sealing members, each second sealing member engaging an end face of a liner.

9. Assembly according to claim 8, wherein the second face of the main body and/or the second cover plate is provided with recesses at the locations of the liner ends for receiving a second sealing member.

10. Assembly according to claim 2 or 3, wherein the first and/or second cover plate is provided with bores extending in line with the bores in the main body, and wherein the first and/or second sealing members are pierceable, such that e.g. a needle can be inserted into each experimentation chamber.

11. Assembly according to claim 6 and/or 8, wherein the first and/or second sealing members are sealing discs.

12. Assembly according to claim 2 or 3, wherein the first and/or second sealing members comprise a filter for filtering the contents of the experimentation chamber upon removal of said contents.

13. Assembly according to claim 12, wherein said first and/or second sealing members comprise an annular seal and a filter extending across the central opening of said seal.

14. A system for performing parallel chemical experiments in particular crystallisation experiments, said system comprising:
- an experimentation assembly according to one or more of the preceding A system for performing parallel chemical experiments, in claims, and
- a filtration device having channels with inlets corresponding to the bores in the main body of the experimentation assembly and a filter in each channel, so that - after removal of the top cover plate of the experimentation assembly when in horizontal position and of the associated sealing member(s) - said filtration device can be brought against the top face of the main body, after which said system is reversed and the contents of the experimentation chambers enters said channels in the filtration device and is filtered.

15. A system according to claim 14, wherein said channels in said filtration device have outlets and wherein said system further comprises a collecting device having collecting chambers with inlets corresponding to the outlets of the filtration device, such that the filtered contents of the experimentation chambers can enter said collecting chambers.

16. A system for performing parallel chemical experiments, in particular crystallisation experiments, said system comprising:
- an experimentation assembly according to one or more of the preceding claims, and
- a press device having multiple press members corresponding to the liners of the experimentation assembly for pressing said liners into and/or out of the main body.

17. A system for performing parallel chemical experiments, in particular crystallisation experiments, said system comprising:

- an experimentation assembly according to one or more of the preceding claims, and
- heating means for heating the content in the experimentation chambers, e.g. for evaporating a solvent or bringing a solid into solution and effecting crystallisation by subsequent cooling.

18. A system according to claim 17, wherein said main body is a solid body of a heat conducting material, preferably a metal, and wherein said heating means are mounted in said main body and/or cover plate(s) or are adapted to contact said main body and/or cover plate(s).

19. A system according to claim 18, wherein the system further comprises a vapour discharge assembly, said assembly comprising multiple hollow needle members, each adapted to be pierced through a sealing member so that vapour discharges via said hollow needle.

20. A system according to claim 19, wherein said needles are upwardly directed and arranged to pierce through the sealing members sealing the bottom face of the experimentation assembly in horizontal orientation.

21. A system according to claim 10, wherein the system further comprises a feed assembly for feeding a substance into the experimentation chambers, said feed assembly comprising at least one hollow needle member adapted to be pierced through a sealing member.

22. A system according to claim 21, wherein said feed assembly is adapted to introduce an anti-solvent into the experimentation chambers.

23. Method for performing parallel chemical experiments, in particular crystallisation experiments, wherein use is made of

an assembly or system according to one or more of the preceding claims.

24. Method for performing parallel chemical experiments, in particular crystallisation experiments, wherein use is made of an assembly system according to claim 14, particular crystallisation experiments, comprising the effecting of crystallisation in the experimentation chambers, and - after removal of the top cover plate of the experimentation assembly when in horizontal position and of the associated sealing member(s) - said filtration device is brought against the top face of the main body, after which said system is reversed and the contents of the experimentation chambers enters said channels in the filtration device and is filtered.

25. Use of an assembly or system according to one or more of the preceding claims for solid form screening of molecules, e.g. salt screening, polymorph screening, enantiomer separation screening, in particular of active pharmaceutical ingredients.

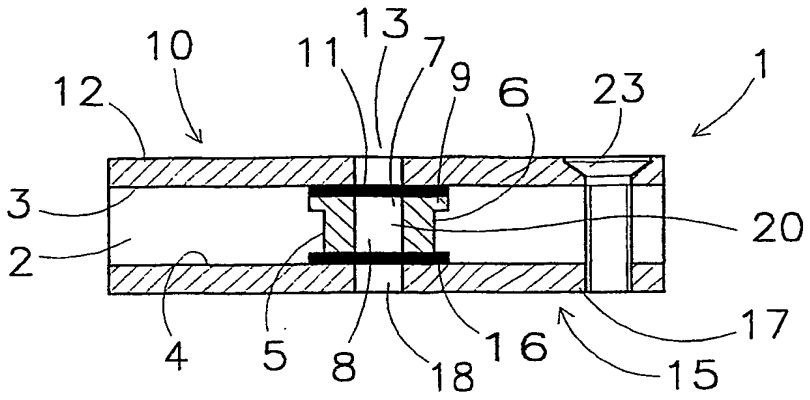

Fig 1

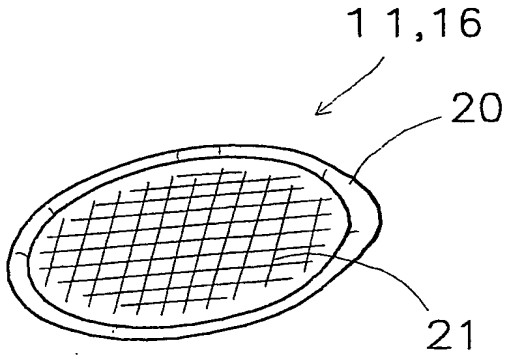

Fig 2

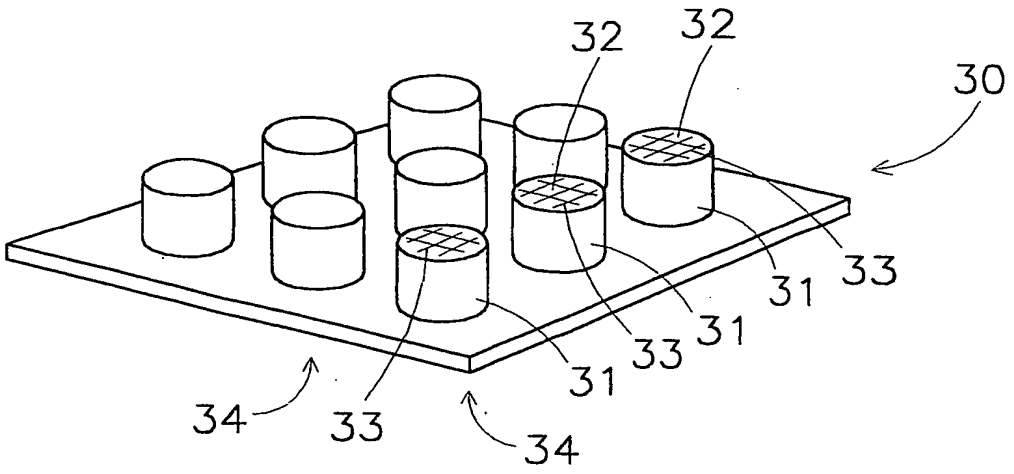

Fig 3

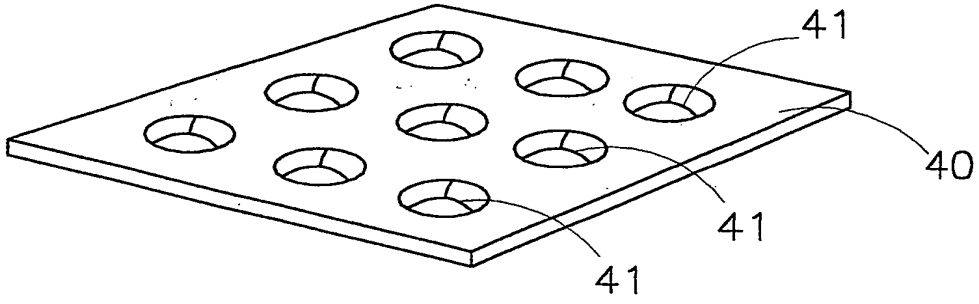

Fig 4

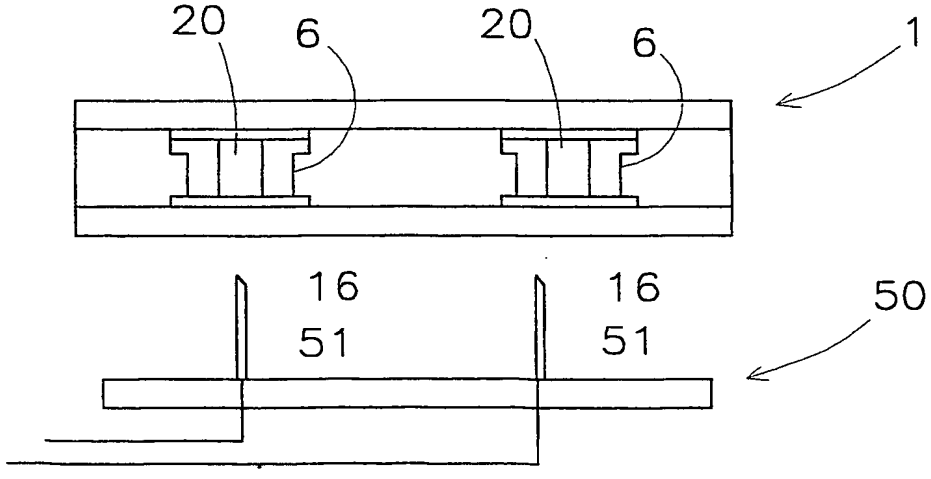

Fig 5

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 866 342 A (KULIKOV NICOLAY ET AL) 2 February 1999 (1999-02-02) column 3, line 59 -column 6, line 43; figures 2-4,4A	1-23,25
A	GB 2 370 797 A (AVANTIUM INTERNAT B V) 10 July 2002 (2002-07-10) page 7, paragraph 2 page 15, last paragraph -page 16, paragraph 1; figure 2E	4,5
A	US 6 054 100 A (STANCHFIELD JAMES E ET AL) 25 April 2000 (2000-04-25) column 6, line 62 -column 7, line 7 column 9, line 56 -column 10, line 25; figures 1,3	10,19-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2003	27/03/2003

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 274 091 B1 (MORRISSEY MICHAEL M ET AL) 14 August 2001 (2001-08-14) column 10, line 65 -column 11, line 6 column 12, line 29-45; figures 1,10-12 ---	10,19,21
A	WO 01 41918 A (ILLUMINA INC) 14 June 2001 (2001-06-14) claim 28 ---	24
A	MCPHERSON A: "CURRENT APPROACHES TO MACROMOLECULAR CRYSTALLIZATION" EUROPEAN JOURNAL OF BIOCHEMISTRY, BERLIN, DE, vol. 189, 1990, pages 1-23, XP000566586 ISSN: 0014-2956 page 7, left-hand column, paragraph 4 -page 8, left-hand column, paragraph 6; figure 9 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 02/00526

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5866342	A	02-02-1999	AU	4705697 A	17-04-1998
			WO	9813137 A1	02-04-1998
			US	6238929 B1	29-05-2001
GB 2370797	A	10-07-2002	WO	02053278 A1	11-07-2002
US 6054100	A	25-04-2000	US	6479020 B1	12-11-2002
			AU	5359398 A	10-06-1998
			EP	0948409 A1	13-10-1999
			GB	2322570 A ,B	02-09-1998
			JP	2000507502 T	20-06-2000
			JP	3338961 B2	28-10-2002
			WO	9822219 A1	28-05-1998
US 6274091	B1	14-08-2001	US	5888830 A	30-03-1999
			AU	7241796 A	09-04-1997
			CN	1197413 A	28-10-1998
			WO	9710896 A1	27-03-1997
			AT	201149 T	15-06-2001
			AU	723605 B2	31-08-2000
			CA	2232505 A1	27-03-1997
			DE	69612866 D1	21-06-2001
			DE	69612866 T2	08-11-2001
			DK	859661 T3	27-08-2001
			EP	0859661 A1	26-08-1998
			ES	2159361 T3	01-10-2001
			GR	3035958 T3	31-08-2001
			IL	123662 A	28-01-2001
			JP	11511381 T	05-10-1999
			PT	859661 T	31-10-2001
WO 0141918	A	14-06-2001	AU	2434401 A	18-06-2001
			EP	1239952 A2	18-09-2002
			WO	0141918 A2	14-06-2001
			US	2002028159 A1	07-03-2002
			US	2002044894 A1	18-04-2002